Safety Evaluation of Toxin Adjuvants Delivered Intranasally

INTRODUCTION

A meeting was convened by Dr. Dennis Lang at the National Institute of Allergy and Infectious Diseases (NIAID) on July 9, 2001 to discuss the safety of proceeding with clinical trials of bacterial toxin adjuvants delivered intranasally. The toxins discussed at the meeting were cholera toxin (CT) and the heat labile enterotoxin (LT) of *E. coli* and attenuated point mutants derived therefrom. The discussion focused on existing preclinical and clinical safety and immunogenicity data and what that data suggest are the best methods and assays to be employed by sponsors in preparing supporting documents for new IND applications. Dr. Marion Gruber from the FDA provided that agency's perspective in an opening lecture.

CT and LT have been shown to be potent oral adjuvants, capable of stimulating particularly strong mucosal immune responses to a variety of antigens in a number of animal models. Moreover, when delivered via the intranasal (IN) route, even better immune responses have been obtained in these same animal models. More than two years ago, clinical trials were just underway to examine the safety and antigenicity of one IN administered mutated toxin adjuvant when some new mouse data indicated that toxins so administered could transit the cribiform plate via olfactory nerve fibers to reach the olfactory bulb and nerves and cause inflammation in the olfactory region of the brain (Bourguignon, P, M. Bisteau, J. Abarca, S. Veenstra, P. Hermand, V. Henderickx, M. Friede, Y. Lobet, and M. Francotte. 1999. Reactogenicity in the nose and the brain of enterotoxins administered intranasally in mice. In *Molecular Approaches to Vaccine Design*, Cold Spring Harbor Laboratory Press, Plainview, New York,p23). In the U.S. human trials were halted until additional preclinical data could be obtained. It was the purpose of this meeting to hear that new data and to discuss the safety of proceeding with human trials. In this paper we present the major findings from the meeting and make recommendations on animal data needed to support new human trials to be done under an investigational new drug application (IND).

Dr. John Clements opened the discussion with an excellent summary of the development of this field. He discussed the structure and enzymatic activity of CT and LT, the mechanism of their enterotoxicity and adjuvanticity, differences in their immunogenicity, and the rationale for exploring various point mutations aimed at attenuating their toxic effects while maintaining their outstanding adjuvant profiles. He also provided an overview of clinical data available on native and mutant LT and introduced the major unresolved issues that were to be discussed at the meeting.

PRECLINICAL EXPERIENCE

Professor Gizurarson provided an overview of experimental animal models that are most commonly used for intranasal delivery studies, the advantages and disadvantages to be considered in selection of the appropriate animal models, and factors affecting successful nasal absorption of drugs in these models, such as anatomical features and physiological conditions of the nose, dosage form(s), and techniques of administration (S. Gizurarson 1990 "Animal models for intranasal drug delivery studies", Acta Pharm. Nord. 2 (2)). While small animal models, such as guinea pigs, hamsters, mice and rats are feasible and relatively inexpensive, these models have certain limitations. For example, because of the small nasal cavities of these animals, they are not optimal for formulation studies, or for determining pharmacokinetic profiles. However, absorption studies can be done in the models.

Dogs and rabbits are particularly useful for conducting pharmacokinetic and formulation studies. Their blood volumes are sufficiently large to permit frequent blood sampling, and allow a full characterization of the absorption and determination of the pharmacokinetic profile of the drug. However, because the olfactory bulb in rabbits and dogs is not easily accessible to the drug, expertise is needed to properly administer the test article so that exposure of the olfactory bulb to the test article is ensured.

Several presentations centered around preclinical safety and immunogenicity studies of intra-nasally administered LT, CT as well as their derivatives conducted in various animal models. The main conclusion that can be drawn from such studies is that the safety and immunogenicity outcomes vary depending on the adjuvant studied, the animal model chosen, and the dose and formulation of the test article. In addition, the results observed after intranasal administration of toxin adjuvants in mice reportedly depended on the strain of mouse chosen. Balb/c mice seem particularly sensitive while CD-1 and other outbred strains are more resistant to the olfactory route of toxin uptake and ensuing inflammatory response.

Dr. Francotte presented data from preclinical studies conducted by Glaxo Smith Kline (GSK) using Balb/c mice. Data showed that in this mouse strain, LT, CT, LTR192G and an LTS63K mutant produced by Dr. Clements were potent intranasal adjuvants, but they also induced severe lesions in the respiratory and olfactory mucosa and overt inflammation of the meninges, the olfactory nerve layer and glomerular layer of the olfactory bulb. Recombinant LTB was a poor intranasal adjuvant. Its administration resulted in low reactogenicity in the nasal cavity and passage into the OB, but no inflammation. Also, LTR192G/G33D, a doubly mutated molecule containing a Gly33 to Asp substitution in the B subunit resulting in lack of GM-1 binding, was a poor intranasal adjuvant with no local reactogenicity and no passage of the molecule into the olfactory bulb (OB). This data suggest that the transport into the OB is GM1-binding dependent.

Dr. Lee of Acambis presented data from pilot studies conducted by Acambis, Inc. of intranasal administration of LT to rats at 100 µg/ml, 50 µl per nostril, 6 doses administered once a week for 6 weeks. Results showed no remarkable findings upon histopathology of the brain (including the forebrain, midbrain, hindbrain and olfactory bulb.). There was subacute inflammation in the submucosa of the respiratory and the olfactory epithelia, but at no time were degeneration or necrosis of olfactory nerves and other structures such as Bowman's glands seen. In cases where the olfactory nerve could be traced through the cribiform plate, there was no evidence of inflammation along the nerve sheaths.

Dr. Giuseppe Del Giudice presented data from preclinical toxicity studies conducted by Chiron using LT mutants completely devoid of enzymatic activity (LTK63) or with some residual enzymatic activity (LTR72). These molecules demonstrated strong adjuvanticity when given intranasally or orally to mice. When LT-K63 was administered intranasally to rabbits, there was no inflammation in the nasal cavity, trachea, lungs, olfactory bulbs, cortex or meninges. Also, preliminary data from studies involving intranasal administration of single and multiple doses of LTK63 and LTR72 mutants and LT (data not presented) in outbred mice (CD-1 strain) indicate no signs of inflammation in olfactory bulbs at any time point from 1 day to 5 months post-intranasal treatment.

Dr. Eldridge of Wyeth Lederle presented data from studies evaluating the safety of a CT mutant, CTE29H, which expresses 1% residual enzymatic activity, administered intranasally in CD-1 mice, as a single dose, in a dose ranging design. Treatment related findings were confined to the nasal cavities, with no findings in the CNS tissue.

Dr. Viret (Berna Biotech Ltd.) reported on the extensive preclinical toxicology studies conducted on a natural LT variant (Escherigen®) used as a mucosal adjuvant in the virosome-formulated intranasal subunit influenza vaccine Nasalfluâ. Toxicological properties were characterized with LT administered alone or as a Nasalflu® component.

In acute toxicity studies in CD-1 mice and Crl:CD(SD)BR rats in which the test article was administered orally or IV, findings were unremarkable at up to 1,000 times the human dose. In repeat dose toxicity studies where baboons were administered Nasalflu or LT intranasally, results demonstrated normal cellular composition of nasal lavages and no evidence of vaccine related inflammation in adjacent neural tissues, i.e., olfactory bulb, optical nerve, hippocampus and other brain structures.

Pharmacokinetic studies with ^{125}I labeled LT administered alone or as a component of Nasalflu were conducted in Balb/c mice, Chacma baboons and various animal species using IN administration. In the baboons, upon necropsy at 72 hours there were small amounts of radioactivity localized in the nasal mucosa,

but larger amounts in the thyroid, corresponding to free iodine, as shown by the fact that accumulation could be totally prevented by adding potassium iodide to drink water in a control experiment in the guinea pig. No radioactivity was detected in the olfactory bulb, optical nerve and brain, as well as in all other organs tested. In Balb/c mice the bulk of radioactivity was rapidly eliminated through the gastro-intestinal and urinary tract upon intranasal delivery of the ^{125}I labeled LT as a component of Nasalflu. In biodistribution studies involving intranasal administration of high specific activity ^{125}I-labeled LT, the amount of radioactivity detected in the olfactory bulb was highly dependent on the animal species since a significant amount was only observed in the olfactory bulb of 3 of 5 Balb/c mice, as opposed to amounts close or equal to baseline level in Black/6 and NMRI mice, and none was observed in rats, guinea pigs, rabbits and the baboon.

Additional pre-clinical trials to measure toxin uptake into tissues was performed in C57Bl/6 mice by Dr. van Ginkel who used ^{125}I-labeled enterotoxins and tetanus toxoid (TT) as a test antigen. Uptake of CT, and CT-B was observed in olfactory nerves and epithelium (ON/E) and the olfactory bulb (OB) but only transiently in lymphoid tissues (NALT, cervical lymph nodes, spleen, and peripheral blood). Binding to nerves and epithelium was GM1 dependent. TT did not target the ON/E or the CNS when given alone but was found in the ON/E (but not the OB or brain) when co-administered with CT as mucosal adjuvant. It was concluded that CT, LT, and CT-B are selectively taken up by the ON/E with retrograde transport to the OB, and when given intranasally as adjuvants, may promote uptake of vaccine proteins into olfactory neurons. In contrast, neither mutants CTE112K or LTE112K lacking ADP- ribosyltransferase activity, redirected ^{125}I-TT to the ON/E. Additionally, when GM1 ganglioside was blocked or other gangliosides targeted by the use of LTIIb, no redirection of TT was observed, indicating that retrograde transport is mediated through GM1 specifically.

In studies using LTR192G, administered intranasally to neonatal gnotobiotic pigs, Dr. Yuan observed that a 5 µg dose of the mLT significantly enhanced the immunogenicity of the rotavirus 2/6-VLP vaccine given concomitantly, yet it did not cause diarrhea or other side effects. However, the mLT adjuvanted VLP vaccine did not induce protective immunity in the gnotobiotic pigs. After evaluation of many combinations, it was determined that protective immunity could be elicited by combined oral attenuated Wa human rotavirus and intranasal Wa 2/6-VLPs with LTR192G. These studies were not designed to look for intranasal transit of vaccine or adjuvant nor did they include an analysis of inflammatory responses in nasal tissue or brain.

CLINICAL EXPERIENCE

Several phase 1 clinical safety studies using intranasally administered recombinant cholera toxin B-subunit were conducted by Dr. Jan Holmgren and colleagues and revealed no visible effects on the nasal mucosa, no systemic

adverse events and no long-term adverse events. Minor side effects included self-limiting increased nasal secretions, itching and sneezing in a dose dependable manner (refer to references on slides). It was concluded that unacceptable side effects (prolonged sneezing and nasal itching) occurred following a dose of 1000 µg delivered IN to volunteers. Doses of 100 or 250 µg were acceptable, however.

Dr. Levine presented results from a Phase 1 safety study conducted with LTR192G. Administration of this adjuvant intranasally at doses of 0.5 and 5 µg to human volunteers resulted in itching, runny nose and sneezing. Sneezing lasting longer than 3 days was observed in 5 out of 6 volunteers receiving 5 µg LT R192G. Local nasal symptoms occurred more frequently among recipients of intranasal LTR192G than among recipients of placebo. Other symptoms such as neck spasm as well as ear/face pain occurred at low rate, were solicited retrospectively after trial discontinuation and an association with LTR192G is unclear. Intranasal LTR192G at these low doses was modestly immunogenic.

Dr. Spyr (Berna Biotech, Ltd.) presented the clinical experience with Nasalflu, an inactivated, virosome-formulated, LT-adjuvanted, intranasal subunit influenza vaccine. The full vaccination consists of 2 daily doses one week apart (daily dose = 7.5 µg of HA, 58.5 µg Lecithin, 2 µg LT from *E. coli*, and PBS ad 200 µl, divided in 2 sprays of 100 µl each, one per nostril). The overall clinical experience comprises a total of 5,469 subjects, 3,820 of these are currently being evaluated. Nasalflu was found to be immunogenic as per the serological EMEA criteria in the seasons 1997-2001, and did induce a mucosal immune response (IgA antibody). The safety of Nasalflu in the clinical trials was determined using a 4-day self-observation period after each dose (day 1 and day 8), followed by a 3-6 week long observation period by the investigator. Subjects recorded solicited and unsolicited symptoms such as nasal discomfort, sneezing, nasal pain, stuffy nose, runny nose, shivering, malaise, nausea, diarrhea, coughing, headache, fatigue and arthralgias. Of the serious adverse events (SAEs) reported in clinical trials 1996-1999, there was 1 hypotensive syncope in 1,800 vaccinees. Of the SAEs reported for approximately 3,600 subjects participating in a clinical (safety) trial in 2000, there were 9 cases of Bell's Palsy (facial paresis) and 1 trigeminal neuralgia that developed into facial paresis. Of the spontaneously reported SAEs since start of sales in October 2000, there were 5 cases of Bell's palsy in approximately 90,000 vaccinees. All of these cases of Bell's Palsy occurred between October 2000 and March 2001 in Switzerland. No cases had been observed during the development program from 1996-1999 with more than 2,100 subjects vaccinated with Nasalflu. An assessment of the Bell's Palsy cases is ongoing.

A detailed analysis of the observed cases did not reveal a distinct pattern for a Nasalflu induced facial paresis. The male-female ratio, recovery time, the side predilection and the benign outcome in almost all cases do not differ from the natural Bell's Palsy course. The latency time was between 2 to 80 days with a

peak at 3-5 weeks. The reported cases were distributed unequally over Switzerland. Such seasonal and geographical peaks have been explained by epidemic outbreaks of a variety of viruses, such as enteroviruses.

In addition to the analysis described above, Berna Biotech Ltd. sponsored a retrospective case-control study to investigate a potential association of Nasalflu vaccination with Bell's palsy in the period of October 2000 to April 2001. In a preliminary analysis, data on the geographical distribution of cases of Bell's Palsy and the Nasalflu doses sold in the 2000/2001-season were compared. It was shown that the highest rates of Bell's Palsy were observed in regions other than those with the largest sales volumes of Nasalflu. This retrospective study is ongoing.

RECOMMENDATIONS

The following represents a summary of opinions and recommendations expressed by the meeting participants regarding study designs for preclinical safety assessments of toxin and toxin derivatives administered intranasally. It does not reflect official FDA policy. As FDA guidance in this area is under development, the reader is encouraged to contact the FDA regarding preclinical toxicity testing requirements for intranasally administered toxins and toxin derivatives to support investigational new drug applications (INDs).

"What additional animal or human data are needed to restart human trials of the IN use of toxin adjuvants in the US?"

There was consensus that additional pre-clinical studies in animal models are needed to evaluate the safety of intra-nasally administered LT and CT adjuvants and derivatives prior to the initiation of clinical trials. Key parameters to be considered in the design of preclinical studies of intra-nasally delivered LT adjuvants are the animal species/strain, anatomy and physiology of the nasal cavity of the particular model, accessibility of the olfactory region/brain, dosage form of the adjuvant, techniques and device of administration, timing of administration, product features, product formulation, appropriate controls, and choice of endpoints to be assessed.

Study design

It was recommended that potential toxicity of the vaccine/adjuvant formulation to be assessed either in a) dedicated-stand alone toxicity studies or in b) combination activity/efficacy studies with toxicity endpoint incorporated into the design of the study. The route of administration should correspond to that intended for use in the clinic, whereby the length of exposure time in the animal model should exceed the one proposed in human. The effect of low, intermediate and high doses of the adjuvant on the animal should be evaluated to establish a "no observed effect limit" (NOEL) in the animal model on which the human dose

is based. The study should include a control arm to study reversibility of potential adverse effects. The exact vaccine/adjuvant formulation intended for clinical use should be studied. Separate toxicity studies using a different route of administration (e.g., IV) may be helpful in understanding the full spectrum of potential toxicity. They should be conducted based on the toxicokinetics relative to adjuvant, if any, or vaccine components. A broad spectrum of information should be obtained including organ weight, clinical chemistry and histopathology. The study should include body weight and food consumption, hematology and chemistry analysis such as liver enzyme levels, serum amylase and serum electrolytes. Data should be collected at frequent intervals, and also following the recovery phase to determine persistence of adverse effects. A complete gross necropsy including organ weights and selected histopathology on organs that may be primarily affected, as well as on organs that may be secondarily affected, should be conducted. Data should be reported in full as the original collection of values and summarized. Toxicity studies should be conducted under GLP.

Animal species and strain

The available preclinical database suggests that animal models differ with regard to their susceptibility to the [toxic/adjuvant] effects of LT and CT and their derivatives. Furthermore, there appears to be strain specific sensitivity in some animal species, i.e., Balb/c versus CD-1, Black/6, or NMRI mice. In general, adverse events were observed to a higher degree in rodent models compared to non-rodent animals and in Balb/c versus outbred strains of mice. There was consensus that for pre-clinical studies the most "sensitive" animal model that would allow extrapolation of findings to humans will need to be chosen. However, since there is uncertainty regarding the animal model that would be most relevant to humans, it may be necessary to address the pre-clinical safety of LT, CT and its derivatives using more than one animal species, and even more than one strain of the same species, e.g. CD-1 mice plus Balb/c mice. To arrive at a risk/benefit assessment, data from both sensitive and refractory animal models will need to be evaluated.

Concern was raised by industry that the regulatory agency may stop a clinical study from moving forward because of adverse findings derived from pre-clinical studies observed in one particular species or strain. FDA representatives discussed that, in order to arrive at a regulatory decision about the pre-clinical safety of a test article, FDA reviews all data available. Thus, an adverse outcome in one animal strain or species may not necessarily prevent a clinical trial from moving forward. The suggestion was made to use two different mice strains, i.e., Balb/c and CD-1 and one other species, such as the guinea pig or a species that is receptive to administration via nasal spray rather than droplets.

The advantages and disadvantages of various species were briefly discussed. Overall, there do not appear to be big differences in the mucosal tissues across species with the exception of hamsters and sheep. The point was made that for

intranasal administration studies, one of the species chosen should be receptive to spray administration of the test article. Rabbits and dogs are useful test models for use of spray devices, however their olfactory bulbs are highly protected and special techniques (and training) are required to ensure that the test article reaches this organ. Monkeys, although generally useful for the study of intranasally delivered adjuvants, may not be a sensitive species to study the effects of enterotoxins. Monkeys differ in their reactogenicity/immunogenicity to enterotoxins in that they may require higher doses. On the other hand, with respect to nasal cavity anatomy and olfactory nerve physiology, monkeys resemble humans much more closely than the other animal species. Under any circumstances, additional work is necessary to establish the monkey as an adequate model for intranasally delivered LT adjuvant and derivatives. FDA discussed that although there may be situations where non-human primates would be the best choice, preclinical testing in non-human primates is not a necessary prerequisite to advance to clinical trials. Mice and rats are useful models for studying intranasal administration of enterotoxin-derived adjuvants because of the observed immunogenicity of these molecules in these models. However, administration of the test article is limited to droplets in these species.

Test article

In response to industry concerns whether GMP material would need to be used to perform preclinical studies FDA commented that for vaccine pre-clinical studies, sufficient information is needed to assure the identity, purity, potency of the product. The product will need to be adequately characterized so that it could support being used in a Phase I clinical trial. It does not need to meet the GMP criteria. The agency recognized that modifications to the product manufacture and dosage are likely as the clinical development progresses. However, there may be situations in which additional pre-clinical safety studies are required. This would depend on the type and amount of changes made during product development. Studies to evaluate the pre-clinical safety of material characterized described above should be performed under GLP conditions as described in 21 CFR 58.

Dose, volume, concentration, and formulation of the test article

Critical parameters affecting the outcome of a preclinical intranasal administration are the dose, volume, concentration, and formulation of the test article. For example, administration of more than 5 ul of test volume per nostril to a mouse would result in the test article being swallowed. Because there are differences among species in the surface area as well as the complexity of the nasal cavities, the dose may need to be adapted either based on weight or surface area of the nasal mucosa. In order to arrive at a pre-clinical dose(s) allowing an extrapolation from one species to other including humans, the following formula was suggested:

$$D_{Animal} = D_{Human} \frac{(W_{Animal})(1/4)\ (3/4)}{W_{Human}}$$

W = weight
D = dose

Reference was made to the following articles describing the best calculation techniques that would allow extrapolation from one species to another:

1. G.B. West, J.H. Brown & B.J. Enquist: A general model for the origin of allometric scaling laws in Biology: Science, 276, 1997 (122-126).
2. G.B. West, J.H. Brown & B.J. Enquist: The fourth dimension of life: fractal geometry and allometric scaling of organisms: Science, 284, 1999 (1677-1679).

Endpoints to be monitored

The following (potential) outcomes that need to be ruled out were discussed:

1. Passage of the toxin into the brain
2. Impact of the presence of the toxin in brain tissues (local reactogenicity)
3. Impact on neurological functions
4. Passage of the co-administered vaccine antigen into the brain

Assays

The following assays were suggested for safety assessment of the toxin adjuvants:

1. Passage of the toxin into the brain

   1.1 'In situ" detection of the toxins in the meninges, the glomerular nerve layer or the olfactory bulb may be performed using immunohistology methods.

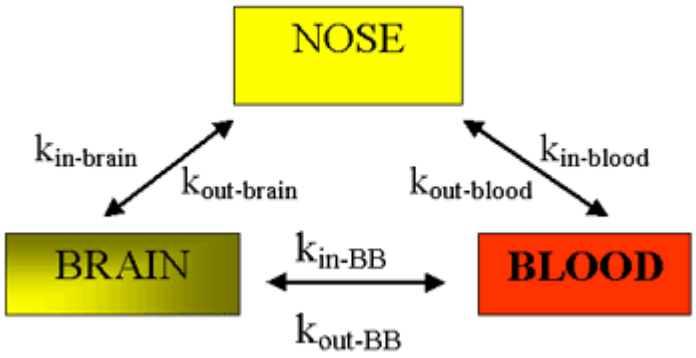
   1.2 Pharmacokinetic studies

   Pharmacokinetic studies may need to be conducted to obtain data regarding the fate of the LT/CT toxins upon intranasal administration. Of particular importance would be to conduct studies to evaluate

absorption of the intranasally delivered toxins by the brain.

Studies to assess the transport of LT/CT toxins into the brain and from the brain (a) via the blood stream and (b) via the nose may need to be conducted to evaluate whether these toxins are absorbed by the brain via systemic circulation and how that may differ from adsorption through the olfactory region (see figure 1 below).

Figure 1



If there is absorption of CT and LT toxins via systemic circulation, conventional toxicology study designs may be used. The establishment of the kinetics of absorption of the molecules via different routes is important. As part of these studies Y1 cell toxicity or GM-1 binding of the molecule may need to be assessed. The use of ^{125}-I labeled CT or LT is discouraged. Instead, the toxins should be labeled using ^{3}H and/or ^{14}C isotopes as long as the corresponding specific activities are high enough for detection (sensitivity issue). Data obtained from studies using toxin molecules labeled with different radioisotopes may need to be compared if results with toxins labeled with one isotope cannot be confirmed using other techniques, e.g., ELISA or immunohistochemical detection. One important internal control to be included in such studies is use of native toxin. Concern was raised that relevant neuroimmunologic assays have not yet been developed to ascertain the safety of the toxin molecules or their derivates using these methods.

2. Impact of the presence of the toxin in brain tissues

   The presence of the toxin in brain tissue and its impacts should be assessed through histological analysis of the lesions (pyknosis, inflammation, perivasculitis, etc).

3. Impact on neurologic functions

   Impacts on neurologic functions as a result of toxin localization in the brain and potential disturbances of neuronal transmission may be assessed through the use of neuroimmunologic assays, olfaction-based neurological assays, and neurological exams, for example the Irwin spectrum which was discussed by Dr. Eldridge. For the sake of comparison, the importance of consistency within the study design in terms of the time at which the sample is taken and the method of sampling for all the potential endpoint assays was discussed.

"Who can or should do this work?"

Ideally, preclinical safety studies to evaluate the safety of intranasally administered LT and CT adjuvants should be conducted using a "central clearing house" to assure consistency and reproducibility in terms of the techniques and controls employed. However, because this may not be a realistic scenario the point was made that at the very least, it is critical to employ a common/controlled set of standards for comparison purposes by companies who conduct preclinical safety testing. The suggestion was made for NIH to sponsor a pre-clinical trial evaluating the safety of LT and derivatives in different animal models and different species. A standard model may be developed in concert with CBER scientists.

"Are these toxins and/or their mutants safe to administer intranasally to humans?"

The clinical safety of intranasally administered CT and LT adjuvants needs further evaluation. In the U.S., only limited clinical experience exists. It was suggested to contact relevant authorities in other countries, i.e., Japan for information on the clinical experiences obtained when these toxins were administered intranasally. Concern was raised regarding how to best assess long term reactogenicity of the molecule in volunteers and potential retrograde transport that may result in neuronal damage. Also, there is the need for neurological exam of the olfactory bulb through clinical parameters.

Available safety data from clinical studies and post-marketing experience in Europe (Switzerland) for Nasalflu, an inactivated, virosome-formulated, LT-adjuvanted, intranasal subunit influenza vaccine raises concerns about a potential association of vaccine administration with observed cases of Bell's Palsy. Although a temporal association has been observed, there is currently no evidence for a causal relationship (study is ongoing). The potential for an induction of facial paralysis due to an adsorption of LT or its derivatives by facial/cranial nerves will need to be evaluated further. Research of the relevant

literature for potential explanation of this phenomena is needed and animal studies to assess if the facial/cranial nerves transport or accumulate CT or LT will need to be conducted.

Attendees

Industry:

Dr. Jean-François Viret, Head of Research Department, SSVI, Berne, Switzerland
Dr. Christian Spyr, Clinical Research Scientist, SSVI. Berne, Switzerland
Dr. John Eldridge, Wyeth Lederle Vaccines, West Henrietta, NY
Dr. Suzanne Laussucq, Associate Director, Clinical Research, Wyeth-Lederle Vaccines
Ms. Sarah Parsons, Wyeth Lederle Vaccines, West Henrietta, NY
Dr. David Clarke, Associate Director, Investigative Toxicology,Wyeth-Ayerst Research
Dr. Yves Lobet, SBBio, Rixensart, Belgium
Dr. Myriam Francotte, SBBio, Rixensart, Belgium
Dr. Giuseppe Del Giudice, Chiron, Siena, Italy
Dr. Cynthia Lee, Acambis, Boston, MA
Dr. Fred Vogel, Aventis Pasteur
Dr. Sveinbjorn Gizurarson, Lyfjathroun hf Research, Reykjavik, Iceland
Dr. Victor Esposito, Chairman and CEO, Antex Biologics, Rockville, MD
Dr. James Jackson, VP Research, Antex Biologics, Rockville, MD

Academic:

Dr. John Clements, Tulane U, New Orleans, LA
Dr. Frits vanGinkel, UAB, Birmingham, AL
Dr. Jerry McGhee, UAB, Birmingham, AL
Dr. Lou Bourgeois, Johns Hopkins, Baltimore, MD
Dr. Mike Levine, UMD, Baltimore, MD
Dr. Karen Kotloff, UMD, Baltimore, MD
Drs. Jan Holmgren and Anna Rudin (in absentia), Goteborg University Sweden
Dr. Robert Edelman, UMD, Baltimore, MD

Government:

Dr. Dennis Lang, DMID, NIAID, NIH
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Dr. Dennis Kopecko, FDA
Dr. Dan Scott, NMRC, Bethesda, MD
Dr. David Tribble, NMRC, Bethesda, MD
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